Optimizing safety and efficacy in radiotherapy for external auditory canal cancer

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Abstract. External auditory canal cancer (EACC) is a rare and aggressive malignancy with no established standard treatment. The present study aimed to investigate the efficacy of radiotherapy (RT) for EACC. The data of 42 patients with EACC treated between January 2000 and August 2023 were retrospectively reviewed. Of these, 10 (24%) patients underwent surgery followed by RT (median dose, 60 Gy), whereas 32 (76%) underwent definitive RT (median dose, 66 Gy) and a total of 23 (72%) patients received concurrent chemotherapy with definitive RT. Overall survival (OS), local control (LC), progression-free survival (PFS) and toxicity were examined. The median age of patients was 65 years, and the median follow-up duration was 31.5 months (range: 6-120 months). In all patients, the 3-year OS, LC and PFS rates were 54.8, 65.5 and 49.0%, respectively. The 3-year OS, LC and PFS rates in patients who underwent surgery followed by RT, and those who underwent definitive RT were 90% vs. 42.9% (P=0.008), 100% vs. 53.9% (P=0.01) and 90% vs. 35.9% (P=0.003), respectively. No local recurrence occurred among those who underwent surgery followed by RT, although 50% of these patients had positive or close surgical margins. Grade ≥3 brain toxicities were observed in 3 (7.1%) patients, all of whom had T4 disease and underwent definitive RT with concurrent systemic chemotherapy. In conclusion, compared with definitive RT, surgery followed by RT was associated with favorable outcomes in patients with EACC. A multidisciplinary approach is crucial for optimizing treatment outcomes, especially for patients in the advanced stages of EACC.

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Abbreviations: CI, confidence interval; CT, computed tomography; CTV, clinical target volume; EACC, external auditory canal cancer; GTV, gross tumor volume; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; LC, local control; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PTV, planning target volume

Key words: EACC, rare cancer, radiotherapy, surgery, chemotherapy

Introduction

External auditory canal cancer (EACC) is a rare and aggressive malignancy that accounts for a small fraction (0.1-0.2%) of head and neck cancers (1). According to national cancer registry data, its annual incidence is estimated to be around 0.1 per 100,000 population in Japan. The management of EACC is characterized by anatomical complexity and a lack of standardized treatment guidelines due to its rarity. The proximity of the external auditory canal to critical structures, such as the facial nerve, temporomandibular joint, and the brain, complicates both surgical resection and high-dose radiation delivery. These factors, combined with challenging diagnostic and metastatic patterns, result in a survival rate that is significantly lower than that of other head and neck cancers, such as pharyngeal cancer. Several retrospective studies have indicated that surgery or radiotherapy (RT) alone may be effective in managing early-stage disease (2,3), whereas a multimodal approach, including surgery, chemotherapy, and RT, is often required for advanced-stage disease (4,5). Traditionally, a combination of subtotal or total temporal bone resection and postoperative RT is considered as the standard of care for resectable tumors (6). However, this approach is highly invasive and may considerably affect the patient's quality of life. Definitive RT is a potentially less invasive alternative

to surgery, particularly for locally advanced or unresectable cases, with the advantage of organ function preservation (7). However, identifying the patient's disease stage remains challenging; the modified Pittsburgh system is the most commonly used (8). Disease stage correlates with survival outcomes, although survival rates vary based on tumor stage. This study addresses the urgent need for evidence-based strategies to optimize RT for EACC.

Materials and methods

Study design and ethics. This retrospective study included patients with EACC who underwent RT at Nagoya City University Hospital and five regional hospitals (Ichinomiya Municipal Hospital, Nagoya Medical Center, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Okazaki City Hospital, and Kariya Toyota General Hospital) between January 2000 and August 2023. This study was approved by the institutional review board of Nagoya City University Hospital (approval no. 60-23-0066). This study was approved by the institutional review boards of five regional hospitals: Ichinomiya Municipal Hospital (approval no. 1388), Nagoya Medical Center (approval no. 2023-436), Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital (approval no. 5042), Okazaki City Hospital (approval no. 2023-53), and Kariya Toyota General Hospital (approval no. 961). The need for written informed consent was waived owing to the retrospective study design, and its content was disclosed in an opt-out form available on the website. This study adhered to the guidelines of the Helsinki Declaration. The eligibility criteria were: i) Pathologically diagnosed EACC, ii) no history of head and neck region irradiation, and iii) no distant organ metastasis. Patients who underwent palliative RT were excluded.

Patient and treatment characteristics. This study included 42 patients with EACC, including 23 men and 19 women with a median age of 65 years (range: 41-89 years) at the time of treatment. The Pittsburgh staging system was used to assess the T-category. Lymph node (N category) and distant (M category) metastases were classified based on the 8th edition of the Union for International Cancer Control tumor, node, and metastasis staging system for head and neck cancers. Patient characteristics are summarized in Table I. A tumor board comprising otorhinolaryngologists, diagnostic radiologists, and radiation oncologists determined the treatment approach.

Surgery. Overall, 10 patients underwent surgery, including lateral (n=8) and subtotal temporal bone resection (n=2). Among these, five patients had clear margins, three had close margins, and two had positive margins. In general, EACC surgery is more invasive than RT. The decision to perform surgery was based on the patient's overall condition and preferences, with surgical candidates being required to have an ECOG performance status ≤2, a maximum tumor diameter ≤3.5 cm, and no distant metastasis. Lateral or subtotal temporal bone resection was decided based on curability and the degree of invasiveness.

Chemotherapy. Of the included patients, 28 underwent systemic chemotherapy. The decision to administer chemotherapy and the regimen were determined based on the patient's condition and concurrent treatment strategy. Concurrent chemotherapy was considered especially for patients in the T3 or advanced stages and 23 patients received concurrent chemotherapy. The decision was made based on the patient's general condition, cardiac and renal function, and preferences. The main regimen was cisplatin-based chemotherapy. Detailed information on the administered regimens is provided in Table I. Intra-arterial chemotherapy was administered at facilities where it was feasible; otherwise, intravenous or oral chemotherapy was administered. All patients receiving the TPF regimen (docetaxel, cisplatin, and 5-fluorouracil) were in the definitive RT group. Among these, five patients received TPF as induction chemotherapy, while two received it as concurrent chemoradiotherapy.

Radiotherapy. Overall, 32 and 10 patients underwent definitive RT and surgery followed by RT, respectively. All included patients underwent RT planned using a computed tomography (CT) based radiation treatment planning system that involved three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). In the definitive RT group, the primary tumor was visualized using CT, magnetic resonance imaging (MRI), and/or ^{18}F-fluorodeoxyglucose positron emission tomography CT (PET-CT) and the gross tumor volume (GTV) was determined. The EACC tumor encompassing the GTV and surrounding tissues was defined as the clinical target volume (CTV). In the postoperative RT group, the tumor bed was visualized on preoperative CT, MRI, and PET-CT images and the tumor-infiltrated area was pathologically confirmed and delineated as the CTV. In both groups, a 5-mm margin was added to the CTV to define the planning target volume (PTV). In general, the target volumes for patients without lymph node metastases excluded the lymph node regions. The CTV in patients with lymph node metastases included the metastatic lymph node levels and adjacent lymph nodes. A 5-mm margin was added to the CTV of the lymph node regions to define the PTV.

Assessment and statistical analyses. Follow-up, including head and neck CT, was performed at 2-month intervals after RT for 6 months and every 2-4 months thereafter. The overall survival (OS), local control (LC), and progression-free survival (PFS) rates were calculated from the time of RT initiation using the Kaplan-Meier method. OS was defined as the time from RT initiation to the last follow-up or all-cause death. LC was defined as the time from RT initiation to local relapse. PFS was defined as the time from RT initiation to recurrence or death and was censored at the last date without events. The log-rank test was used to compare Kaplan-Meier curves. Univariate analyses were conducted using the Cox proportional hazards model to identify factors associated with OS, LC, and PFS. No multivariate analysis was conducted because of the limited sample size. The difference in the patient characteristics of the definitive and postoperative RT groups was investigated using the Student's t-test or Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables. Toxicity was assessed using the Common Terminology Criteria for Adverse Events version 5.0. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Patient and treatment characteristics.

Characteristic	Value
Median age, years (range)	65 (41-89)
Sex, n (%)	
Male	23 (55%)
Female	19 (45%)
Performance status, n (%)	
0	13 (31%)
1	21 (50%)
2	7 (17%)
3	1 (2%)
Histological subtype, n (%)	
SCC	39 (93%)
ACC	2 (5%)
BCC	1 (2%)
T classification	
T1	4 (10%)
T2	7 (17%)
T3	18 (42%)
T4	13 (31%)
N classification	
N0	39 (93%)
N1	3 (7%)
Stage, n	
I	4 (9%)
II	7 (17%)
III	16 (38%)
IV	15 (36%)
Treatment modality, n (%)	
Surgery + PORT	10 (24%)
Definitive RT	32 (76%)
Surgery technique	
Lateral temporal bone resection	8 (80%)
Subtotal temporal resection	2 (20%)
RT technique, n (%)	
Surgery + PORT, 3D-CRT/IMRT	6 (60%)/4 (40%)
Definitive RT, 3D-CRT/IMRT	9 (28%)/23 (72%)
Median RT dose, Gy (range)	66 (47.5-70)
Chemotherapy, n (%)	
Concurrent IA CDDP	10 (23%)
Three courses, 100/200 mg/m^2	2/4
Four courses, 100/200 mg/m^2	3/1
Concurrent IV CDDP	7 (17%)
Three triweekly courses, 80/100 mg/m^2	3/4
TPF	7 (17%)
Induction/concurrent	5/2
Concurrent Cmab	2 (5%)
Concurrent S-1	2 (5%)
None	14 (33%)

SCC, squamous cell carcinoma; ACC, adenoid cystic carcinoma; BCC, basal cell carcinoma; PORT, postoperative radiotherapy; RT, radiotherapy; 3DCRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; IA CDDP, intra-arterial cisplatin; IV CDDP, intra-venous cisplatin; TPF, docetaxel-cisplatin-fluorouracil (50-60-700 mg/m^2, two courses); C-mab, cetuximab (250 mg/m^2, six courses); S-1, tegafur/gimeracil/oteracil (80-100 mg/m^2 per day, orally on days 1 to 14 and 29 to 42).

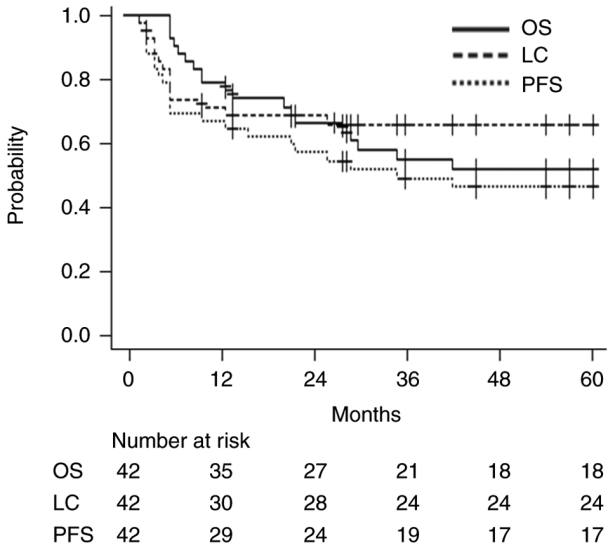

Figure 1. OS, LC and PFS curves for all patients. LC, local control; OS, overall survival; PFS, progression-free survival.

All statistical analyses were conducted using R version 4.4.0 (The R Foundation for Statistical Computing, Vienna, Austria), an open-source software.

Results

Outcomes and prognostic factors. The median follow-up period of the 42 patients was 31.5 months (range: 6-120 months). Of the included patients, 14 died of the primary disease and 5 died of other causes. These five deaths from other causes consisted of one patient in the postoperative RT group (due to pneumonia) and four patients in the definitive RT group (due to pneumonia, heart failure, and other comorbidities). Recurrence was reported in 16 patients, including 14 with local recurrence, 5 with cervical lymph node recurrence, and 5 with distant organ metastases. Four of the seven patients (57%) who underwent the TPF regimen achieved local control without recurrence. The median interval from local recurrence to death was 4 months (range: 1-68 months). In all patients, the 3-year OS, PFS, and LC rates were 54.8% (95% confidence interval [CI]: 41.2-73.0%), 49.0% (95% CI: 37.7-69.1%), and 65.5% (95% CI: 54.1-83.7%), respectively, and the median survival duration was 42 months. Fig. 1 presents the OS, LC, and PFS curves for all 42 patients. Table II summarizes the prognostic factors on univariate analyses for OS, LC, and PFS. Univariate analyses revealed that the treatment method was a significant prognostic factor (surgery followed by RT vs. definitive RT: OS: hazard ratio [HR]: 9.60, 95% CI: 1.27-72.5, P=0.028; LC: HR: 12.22, 95% CI: 1.62-156.4, P=0.008; PFS: HR: 11.54, 95% CI: 1.54-86.5, P=0.017).

Comparison of patient characteristics and outcomes of the postoperative and definitive RT groups. Overall, 2 patients in T2 stage and 8 in T3/T4 stage underwent surgery followed by RT. None of them had lymph node metastases, whereas 5 (50%) patients underwent concurrent systemic chemotherapy. In contrast, 9 patients in T1/T2 stage and 23 in T3/T4 were included in the definitive RT group. Of these, 3 had lymph

Table II. Univariate analyses of OS, LC and PFS.

	OS			LC			PFS		
Variable	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age, years									
<60 (n=15)	1.00	-	-	1.00	-	-	1.00	-	-
≥60 (n=27)	1.88	0.68-5.24	0.22	1.13	0.38-3.34	0.82	1.37	0.56-3.38	0.48
Performance status									
0 and 1 (n=34)	1.00	-	-	1.00	-	-	1.00	-	-
2 and 3 (n=8)	1.68	0.61-4.69	0.32	1.89	0.59-6.01	0.28	1.32	0.48-3.58	0.58
T classification									
1 and 2 (n=11)	1.00	-	-	1.00	-	-	1.00	-	-
3 and 4 (n=31)	1.04	0.39-2.74	0.94	6.48	0.84-49.5	0.072	1.34	0.52-3.43	0.54
Treatment methods									
Surgery + PORT (n=10)	1.00	-	-	1.00	-	-	1.00	-	-
Definitive RT (n=32)	9.60	1.27-72.5	0.028	12.22	1.62-156.4	0.008	11.54	1.54-86.5	0.017
RT dose, Gy									
<60 (n=5)	1.00	-	-	1.00	-	-	1.00	-	-
≥60 (n=37)	1.51	0.35-6.55	0.58	2.22	0.29-17.02	0.44	1.84	0.43-7.90	0.41
RT technique									
3D-CRT (n=15)	1.00	-	-	1.00	-	-	1.00	-	-
IMRT (n=27)	1.20	0.47-3.06	0.69	1.64	0.51-5.28	0.40	1.49	0.60-3.67	0.38
Chemotherapy									
Yes (n=28)	1.00	-	-	1.00	-	-	1.00	-	-
No (n=14)	1.11	0.44-2.84	0.81	0.72	0.22-2.30	0.58	0.97	0.41-2.33	0.95

OS, overall survival; LC, local control; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; PORT, postoperative radiotherapy; RT, radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy.

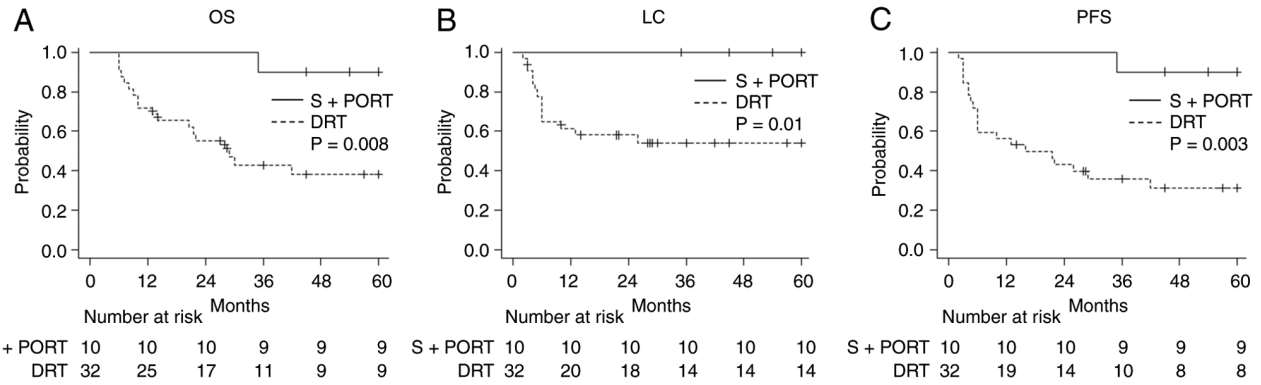

Figure 2. (A) OS curves for S combined with PORT and DRT. (B) LC curves for S combined with PORT and DRT. (C) PFS curves for S combined with PORT and DRT. DRT, definitive radiotherapy; LC, local control; OS, overall survival; PFS, progression-free survival; PORT, postoperative radiotherapy; S, surgery.

node metastases and 29 patients did not. Moreover, 23 (72%) patients underwent concurrent systemic chemotherapy in definitive RT. The patient and treatment characteristics of the postoperative and definitive RT groups are summarized in Table III. Compared with the definitive RT group, the postoperative RT group had a significantly smaller PTV and received a lower RT dose (median PTV: 71 cm^3 vs. 87 cm^3, P=0.021; median RT dose: 60 Gy vs. 66 Gy, P=0.004). The 3-year OS, LC, and PFS rates in the postoperative and definitive RT groups were 90% vs. 42.9%, 100% vs. 53.9%, and 90% vs. 35.9%, respectively. P-values determined using the log-rank test were 0.008, 0.01, and 0.003, respectively. Fig. 2 presents the OS, LC, and PFS curves for both groups.

Toxicities. After RT, 1 (2.4%) patient developed grade 3 brain necrosis and 2 (4.7%) developed grade 3 and 4 brain abscesses. All three T4 patients who developed severe toxicities were treated with IMRT in the definitive RT group

Table III. Patient characteristics of the surgery combined with PORT group and definitive RT group.

Characteristic	Surgery + PORT (n=10)	Definitive RT (n=32)	P-value
Median age, years (range)	65 (41-77)	65 (43-89)	0.43
Sex, male/female	6/4	17/15	1.0
Performance status, 0/1/2/3	1/7/2/0	12/14/5/1	0.32
T classification, T1/T2/T3/T4	0/2/6/2	4/5/12/11	0.55
N classification, N0/N1	10/0	29/3	1.0
Median PTV, cm^3 (range)	71 (41.3-114)	87 (14.4-350)	0.021
RT technique, 3D-CRT/IMRT	6/4	9/23	0.69
Median RT dose, Gy (range)	60 (47.5-70)	66 (50-70)	0.004
Chemotherapy, use/non-use	5/5	23/9	0.25

PORT, postoperative radiotherapy; RT, radiotherapy; PTV, planning target volume; 3D-CRT, 3-dimensional conformal radiotherapy.

Table IV. Studies of radiotherapy for external auditory canal cancer.

First author, year	n	T stage	Treatment modality	OS	LC or PFS	Toxicity (≥Grade 3)	(Refs.)
Fujiwara, 2015	13	T3: 1; T4: 12	DRT: 13	58.7% (2-year)	53.8% (PFS, 2-year)	15%	(10)
Koto, 2016	13	T3: 4; T4: 9	DRT: 13 (carbon ion)	40% (3-year)	54% (LC, 3-year)	15%	(11)
Choi, 2017	32	T1-2: 12; T3-4: 20	S + RT/DRT: 21/11	57% (5-year)	52% (PFS, 5-year)	0	(12)
Matoba, 2018	25	T1-2: 9; T3-4: 16	S/DRT/C: 16/7/2	75.8% (2-year)	58% (PFS, 2-year)	NA	(13)
Hayashi, 2019	31	T1-2: 6; T3-4: 25	DRT: 31 (carbon ion)	58.7% (3-year)	55% (LC, 3-year)	6.5%	(14)
Nagano, 2019	21	T3: 8; T4: 13	S+RT/DRT: 13/8	62% (2-year)	71% (LC, 2-year)	4.8%	(15)
Shiga, 2021	74	T3: 8; T4: 66	DRT: 74; TPF: 50; CDDP: 24	DRT: 54.6% (5-year); TPF: 64.4% (5-year); CDDP: 36.7% (5-year)	DRT: NA; TPF: NA; CDDP: NA	NA	(16)
Laskar, 2022	89	T1-2: 16; T3-4: 73	S + RT/DRT: 65/24	63.5% (5-year)	66.2% (LC, 5-year)	NA	(17)
Jang, 2023	51	T1-2: 19; T3-4: 32	S or S + RT/DRT: 41/10	64% (5-year)	71% (PFS, 5-year)	NA	(18)
Ooka, 2025	73	T1-2: 37; T3-4: 36	S + RT/DRT: 61/12	86.6% (3-year)	81.9% (PFS, 3-year)	NA	(19)
Zhang, 2025	173	T1-3: 46; T4: 127	S + RT:173	80.6% (5-year)	72.7% (PFS, 5-year)	1.2%	(20)
Present study	42	T1-2: 11; T3-4: 31	S + RT/DRT: 10/32	54.8% (3-year)	65.5% (LC, 3-year)	7.1%	

OS, overall survival; LC, local control; PFS, progression-free survival; S, surgery; C, chemotherapy; RT, radiotherapy; DRT, definitive radiotherapy; NA, not available.

and received 70 Gy with concurrent systemic chemotherapy. Toxicity occurred at 2, 12, and 17 months after RT. Of the two patients with brain abscesses, one was conservatively treated with antibiotics and the other underwent brain surgery. The case of the patient who underwent surgery for brain abscess has been reported in detail (9). Other toxicities ≥grade 3 did not occur.

Discussion

The results of this study suggest that surgery followed by RT is associated with more favorable treatment outcomes than definitive RT in patients with EACC. Table IV summarizes previous studies on RT for EACC (10-20). Regarding the different outcomes for the patients in the postoperative and

definitive RT groups, the treatment modality used may affect prognosis. Several factors may contribute to this difference in outcomes. The outcomes of surgery combined with postoperative RT vs. definitive RT are controversial, with one report suggesting that surgery followed by RT is better, (17) whereas another reported no difference between the groups (21). However, it is crucial to acknowledge the potential selection bias that is inherent in this retrospective study design. In our study, although the definitive and postoperative RT groups primarily included patients in T3/4 stages, those selected for surgery likely possessed more favorable baseline characteristics (e.g., more localized invasion or better general condition). Therefore, the favorable outcomes observed in the group that underwent surgery followed by RT must be interpreted with caution as they likely reflect patient selection rather than treatment modality efficacy itself.

A study on completely resected early-stage EACC reported that administering postoperative RT does not provide an additional benefit, with no significant difference in the 5-year disease-free survival of patients who underwent surgery followed by RT and those who did not undergo RT (3). The superiority of surgery followed by RT may be related to the reduction in tumor volume through surgical resection and effective irradiation of microscopic disease, as well as precise RT planning based on pathological information such as margin status and invasion depth. Matoba *et al* reported that surgery alone or surgery followed by RT tended to have better treatment outcomes than definitive RT for patients with advanced-stage disease (13). A study including a larger number of patients reported that surgery followed by RT is associated with improved outcomes compared with definitive RT (17). A favorable 5-year OS rate of 80.6% was reported in the group that underwent surgery combined with preoperative or postoperative RT (20). Positive surgical margins are considered a risk factor for local recurrence and a poor prognostic factor for patients who underwent surgery followed by RT (22). Although 50% of patients in the postoperative RT group in our study, including advanced-stage cases, had positive or close margins, their outcomes were good. This study reports that no local recurrence was observed in the postoperative RT group, even in patients with positive/close margins (50% of the cohort), suggesting that postoperative RT effectively eliminates microscopic residual disease. These findings support reducing the PTV margin in postoperative RT to minimize toxicity while maintaining efficacy.

In the definitive RT group, the median time from local recurrence to death was short at 4 months, emphasizing the importance of LC. In advanced cases, hypoxic tumor regions may reduce radiosensitivity and limit the efficacy of definitive RT to cover the entire tumor (23). Carbon ion RT can be administered to improve LC for EACC; however, RT alone cannot achieve sufficient LC (11). This suggests that merely increasing the intensity of RT is insufficient, indicating the importance of chemotherapy. In this study, 23 patients in the definitive RT group received concurrent chemotherapy but under different regimens. EACC is a rare type of cancer; thus, no standard chemotherapy regimen has been established, and platinum-based treatments similar to those for head and neck squamous cell carcinoma are often currently used. Recently, TPF therapy, which combines docetaxel, cisplatin, and fluorouracil, has been used as a concurrent chemoradiotherapy regimen, with reports suggesting its contribution to high response rates and improved survival (24). Further data validation in large cohorts is warranted to confirm their efficacy and safety. Studies have reported achieving good control with cetuximab as the most prevalent histological type of head and neck cancer including EACC is the squamous cell carcinoma (25,26). However, optimal drug selection, dosage, and timing (concurrent, induction, adjuvant, etc.) remain unclear. The findings of this study could not clarify the specific role or optimal content of chemotherapy in definitive RT. Furthermore, immunoradiotherapy is another promising treatment. The synergistic mechanisms of programmed cell death-1 inhibitors and RT, which can activate systemic anti-tumor immunity, were reviewed (27). For rare malignancies like EACC, where definitive RT alone often fails to achieve sufficient local control in advanced stages, the addition of agents such as pembrolizumab could theoretically improve outcomes. In the future, multi-institutional collaborative research to identify the molecular biological characteristics of EACC and conduct clinical trials to establish more effective chemotherapy regimens with fewer side effects is important to improve definitive RT outcomes.

The serious adverse event of brain abscess is another concern. In this study, grade 3 and 4 brain abscess were observed in two (4.7%) patients. Both were patients in the T4 stage who had undergone definitive RT (70 Gy) and concurrent chemotherapy. Brain abscess is a life-threatening, serious late adverse event that significantly reduces the patient' quality of life. The irradiation field often encompasses the brain parenchyma and meninges as the tumor infiltrates the temporal bone and skull base in the T4 stage. The incidence of central nervous system infections is higher after RT in patients with nasopharyngeal carcinoma with a compromised central nervous system barrier, a condition frequently caused by high chronic otitis media prevalence (28,29). Thus, the synergistic effect of high-dose radiation and chemotherapy decreased the tolerance of normal tissues and increased the risk of infection. However, not all patients with skull base invasion develop brain abscesses after the definitive RT. Specific causative factors for early-onset brain abscess after definitive RT for EACC remained unclear in these cases. IMRT is useful for improving dose conformity and reducing the risk of toxicity (30-32). Recently, there's been an increase in head and neck cancer patients receiving particle therapy (33). Regarding future directions, carbon ion RT is an emerging modality for EACC. While the integration of carbon ion RT into postoperative RT strategies could theoretically enhance local control, this approach warrants extreme caution. Given the high relative biological effectiveness of carbon ions, the potential for severe late toxicities such as brain necrosis or cranial nerve injury, must be carefully weighed, especially when irradiating the surgical bed where anatomical barriers may be compromised. Therefore, careful patient selection and precise dose constraints are mandatory before carbon ion RT combined with postoperative RT can be considered a viable clinical option. Moreover, combining high-dose irradiation and chemotherapy in advanced cases carries the risk of serious complications such as brain abscess. Therefore, treatment indications, dose, and chemotherapy intensity must

be carefully determined. Furthermore, close post-treatment follow-up for early detection and appropriate intervention is crucial.

This study has several limitations. First, the retrospective study design is subject to potential selection bias, which can be particularly pronounced in rare cancers. Second, the limited number of patients precluded a multivariate analysis, emphasizing the need for a larger sample size for more detailed investigation, especially since the postoperative RT group included a very small number of patients. Third, the extended recruitment period, spanning 23 years, resulted in chronological changes in treatment methodologies. Fourth, the concurrent chemotherapy regimens were heterogeneous. While these agents differ in their mechanisms of action and treatment intensity, the small sample size precluded a detailed analysis of the efficacy of each specific regimen. In conclusion, surgery followed by RT was associated with more favorable outcomes than definitive RT in patients with EACC. We suggest a stratified treatment approach. For T1-T2 stage, definitive RT remains a viable option, offering the benefit of organ preservation. However, for T3-T4 stage, surgery followed by postoperative RT may be considered as a primary strategy to mitigate the high risk of local failure associated with definitive RT. A multidisciplinary approach is crucial for optimizing treatment outcomes, especially in patients in advanced stages. Hence, future prospective studies are warranted to establish the optimal treatment method.

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Availability of data and materials

The data generated in the present study are not publicly available due to restrictions such as their containing information that could compromise the privacy of research participants, but may be requested from the corresponding author.

Authors' contributions

YI, TT, NT and AH conceptualized the study. MK, AM, CS, SO, KU, DO, MN, TM, DK and SI conducted the investigation and data acquisition. AT, NK, MO and ST performed the formal analysis. YI wrote the original draft. TM, DK, SI and AH performed review and editing. YI and TT confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was performed after approval by the institutional review board of Nagoya City University Hospital (approval no. 60-23-0066). This study was approved by the institutional review boards of five regional hospitals: Ichinomiya Municipal Hospital (approval no. 1388), Nagoya Medical Center (approval no. 2023-436), Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital (approval no. 5042), Okazaki City Hospital (approval no. 2023-53), and Kariya Toyota General Hospital (approval no. 961). Written informed consent was waived due to the retrospective nature of this study, its content was disclosed in an opt-out form available on the website. This study has been conducted in compliance with the guidelines of the Helsinki Declaration.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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